

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
3 January 2002 (03.01.2002)

PCT

(10) International Publication Number
WO 02/00195 A2

- (51) International Patent Classification⁷: A61K 9/12, A61P 23/02, 25/04
- (21) International Application Number: PCT/US01/20322
- (22) International Filing Date: 26 June 2001 (26.06.2001)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
60/222,164 26 June 2000 (26.06.2000) US
- (71) Applicant: EPICEPT CORPORATION [US/US]; 270
Sylvan Avenue, Englewood Cliffs, NJ 07632 (US).
- (72) Inventors: WILLIAMS, Robert, O.; 4514 Rapid Springs
Cove, Austin, TX 78746 (US). ZHANG, Feng; 4559 Av-
enue A #204, Austin, TX 78751 (US). KOLENG, John, J.;
3002 Boxdale Drive, Austin, TX 78757 (US). PASTER-
NAK, Gavril, W.; Apartment 21M, 500 East 83rd Street,
New York, NY 10028 (US). KOLESNIKOV, Yuri, A.; 4
Esmond Place, Tenafly, NJ 07670 (US).
- (74) Agents: ABRAMS, Samuel, B. et al.; Pennie & Edmonds
LLP, 1155 Avenue of the Americas, New York, NY 10036
(US).
- (81) Designated States (*national*): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,
CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM,
HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK,
LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX,
MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL,
TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW.
- (84) Designated States (*regional*): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian
patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European
patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE,
IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF,
CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).
- Published:**
— without international search report and to be republished
upon receipt of that report
- For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.*

(54) Title: METHODS AND COMPOSITIONS FOR TREATING PAIN OF THE MUCOUS MEMBRANE

(57) Abstract: Compositions useful for long-lasting pain relief from mucosal damage, such as mucosal inflammation, abrasions, ulcerations, lesions, trauma and incisions, without significant systemic absorption. The compositions of the invention are particularly suitable for application to the mucous membrane of the nasal cavity and bucal cavity. To relieve pain, the compositions or the invention are topically applied directly to the affected area.

WO 02/00195 A2

METHODS AND COMPOSITIONS FOR TREATING PAIN OF THE MUCOUS MEMBRANE

FIELD OF THE INVENTION

The invention relates to methods and compositions for treating the pain associated with mucosal damage, such as inflammation, abrasions, ulcerations, lesions, incisions, and trauma.

BACKGROUND OF THE INVENTION

The term mucous membrane refers to the moist linings of the buccal cavity, nasal cavity, gastrointestinal tract, respiratory tract, conjunctiva, vagina, colon, urinary bladder, and urethra (Forstner *et al.*, 1973 *J. Cell. Sci.* 12:585; Peppas *et al.*, 1985 *J. Control. Release* 2:257; Lehr *et al.*, 1992 *J. Control. Release* 18:249; Spiro, 1970 *Ann. Rev. Biochem.* 39:599; Lebat-Robert *et al.*, 1979 *Path. Biol.* 24:241). The normally smooth, moist, and pink buccal mucosa is very sensitive and inflammation or ulceration (oral mucositis) causes severe pain. Dental surgery, such as root canal and tooth extraction can also severely damage the buccal mucosa causing severe pain. Moreover, oral mucositis and dental surgery can induce secondary conditions, such as weight loss and dehydration from reluctance to eat or drink, infection (bacterial, fungal, and viral), fever, nausea, and diarrhea.

Oral mucositis has a variety of causes, for example, bacterial infections, such as streptococci; viral infections, such as herpes simplex virus; fungal infections; side effects of systemic diseases; vitamin deficiency; iron deficiency; cheek biting; mouth breathing; jagged teeth; orthodontic appliances; ill-fitting dentures; excessive use of alcohol or tobacco; thermally-hot foods; spicy foods; and as a side effect of medication. Severely-painful oral mucositis is a symptom endured by almost all chemotherapy patients.

Mucositis symptoms peak 7 to 10 days following chemotherapy, and gradually recede over the following two weeks. For a discussion of the causes and symptoms of mucositis, see *The Merck Manual, Fifteenth Edition*, Merck Sharp & Dohme Research Laboratories, Rahway, NJ, (1987) pp. 2322-2320.

Topical application of local anesthetics can provide some relief of oral-mucositis and dental-surgery pain but absorption through the mucous membranes occurs rapidly, and pharmaceuticals applied to the mucous membrane for their local effect sometimes cause systemic toxicity (Goodman and Gilman's *The Pharmacological Basis of Therapeutics* 9th ed. J. G. Harman and L. E. Limird Eds., McGraw-Hill New York 1996 p. 8) especially with the higher doses required for adequate pain relief. Systemic absorption is even more likely when the mucous membrane is ulcerated or inflamed. Thus, with traditional anesthetic compositions for mucositis, e.g., 2 percent lidocaine oral rinse or 5% lidocaine ointment, systemic toxicity limits the dosage and so adequate pain relief is difficult to achieve. Other

less toxic pain relieving compositions, such as rinses comprising hydrogen peroxide and sodium bicarbonate are less effective at reducing pain. An additional problem with oral rinses is, that following application, the action of swallowing and saliva reduces the concentration of active agent on the affected area, thus oral rinses comprising local anesthetics have a low duration of activity.

5 In summation, a long-lasting, non-toxic anesthetic composition effective for amelioration of the severe pain induced by mucosal damage, such as mucositis and dental surgery, is needed.

SUMMARY OF THE INVENTION

10 In one aspect, the invention provides compositions and methods that provide long-lasting local anesthesia and effective pain relief. The compositions of the invention can be topically applied to the affected area, for example, via a dose-metered applicator adapted for spraying or adapted for use with a cannula. When topically applied, the compositions of the invention provide a powerful local-anesthetizing effect, in spite of low anesthetic
15 concentration. Hence, the compositions of the invention provide significant pain relief with low systemic absorption and, therefore, low systemic toxicity. The compositions of the invention, in addition to the ability to remain on the affected area for extended periods, hydrate and soothe.

In one embodiment, the compositions of the invention can be topically applied directly to the affected area to alleviate pain in a subject on any area of a subject's body.
20

In another embodiment, the compositions of the invention are useful for topical application to a subject's mucous membrane, to induce a long-lasting local-anesthetic effect, thereby relieving pain from mucositis, such as mucosal inflammation, abrasions, ulcerations, and lesions, without significant systemic absorption.

25 In yet another embodiment, the compositions of the invention are useful for topical application to the site of dental surgery, such as root-canal or tooth-extraction surgery, to induce a long-lasting local-anesthetic effect, thereby relieving the surgical pain, without significant systemic absorption.

In one more embodiment, the invention relates to compositions comprising a mucoadhesive, a local anesthetic or a pharmaceutically-acceptable salt thereof, and an
30 opioid or a pharmaceutically-acceptable salt thereof. In a preferred embodiment, the compositions contain water and are sterile. In a more preferred embodiment, the compositions of the invention, further comprise a chelating agent and a preservative.

In another embodiment, the invention relates to a container adapted for topical
35 application and containing a pharmaceutically-acceptable composition comprising a mucoadhesive, a local anesthetic or a pharmaceutically-acceptable salt thereof, and an opioid or a pharmaceutically-acceptable salt thereof. Preferably, the container is adapted

for dose-metered application, such as a dose-metered pump for use with a spray applicator or cannula.

In still another embodiment, the invention relates to a method of inducing local anesthesia in a subject's mucosal membrane by topically applying a pharmaceutically-acceptable composition comprising a local anesthetic or a pharmaceutically-acceptable salt thereof and an opioid or a pharmaceutically-acceptable salt thereof to the subject's mucosal membrane. Preferably, the composition is applied to an area within the subject's buccal or nasal cavity. Preferably, the composition further comprises a mucoadhesive.

In yet another embodiment, the invention relates to a method of inducing local anesthesia in a subject by topically applying a composition comprising a mucoadhesive, a local anesthetic or a pharmaceutically-acceptable salt thereof, and an opioid or a pharmaceutically-acceptable salt thereof to a subject. Preferably, the composition is applied to a mucosal surface of the subject, for example, an area within the subject's buccal or nasal cavity.

These and other features, aspects, and advantages of the invention will become better understood with reference to the following detailed description, examples, and appended claims.

DETAILED DESCRIPTION OF THE INVENTION

The phrase "pharmaceutically-acceptable salt(s)," as used herein includes but is not limited to salts of acidic or basic groups that may be present in compounds used in the present compositions. Compounds included in the present compositions that are basic in nature are capable of forming a wide variety of salts with various inorganic and organic acids. The acids that may be used to prepare pharmaceutically-acceptable acid addition salts of such basic compounds are those that form non-toxic acid addition salts, *i.e.*, salts containing pharmacologically acceptable anions, including, but not limited to, sulfuric, citric, maleic, acetic, oxalic, hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate, bisulfate, phosphate, acid phosphate, isonicotinate, acetate, lactate, salicylate, citrate, acid citrate, tartrate, oleate, tannate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisinate, fumarate, gluconate, glucaronate, saccharate, formate, benzoate, glutamate, methanesulfonate, ethanesulfonate, benzenesulfonate, *p*-toluenesulfonate and pamoate (*i.e.*, 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)) salts.

Compounds included in the present compositions that include an amino moiety may form pharmaceutically-acceptable salts with various amino acids, in addition to the acids mentioned above. Compounds, included in the present compositions, that are acidic in nature are capable of forming base salts with various pharmacologically acceptable cations. Examples of such salts include alkali metal or alkaline earth metal salts and, particularly, calcium, magnesium, sodium, lithium, zinc, potassium, and iron salts. For a review on

pharmaceutically-acceptable salts see Berge *et al.*, 1977 *J. Pharm. Sci.*, 66:1, incorporated herein by reference.

As used herein the term "opioid" means all agonists and antagonists of opioid receptors, such as mu (μ), kappa (κ), and delta (δ) opioid receptors and subtypes thereof. For a discussion of opioid receptors and subtypes see *Goodman and Gilman's The Pharmacological Basis of Therapeutics* 9th ed. J. G. Harman and L. E. Limbird Eds., McGraw-Hill New York:1996 pp. 521-555, incorporated herein by reference. The opioid can be any opioid receptor agonist or antagonist known or to be developed. Preferred opioids interact with the μ -opioid receptor, the κ -opioid receptor, or both. Preferably, the opioid is an opioid-receptor agonist.

Examples of suitable opioids for use with the invention include, but are not limited to, alfentanil, allylprodine, alphaprodine, anileridine, benzylmorphine, benzitramide, norbinaltorphimine, bremazocine, buprenorphine, butorphanol, clonitazene, codeine, CTOP, DAMGO, desomorphine, dextromoramide, dezocine, diampromide, dihydrocodeine, dihydrocodeine enol acetate, dihydromorphine, dimenoxadol, dimepheptanol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, diprenorphine, DPDPE, eptazocine, ethoheptazine, ethylketocyclazocine, ethylmethylthiambutene, etonitazene, etorphine, fentanyl, hydrocodone, hydromorphone, hydroxypethidine, isomethadone, ketobemidone, levorphanol, lofentanil, loperamide, meperidine, meptazinol, metazocaine, methadone, metopon, morphine, myrophine, nalbuphine, naltrindole, benzoylhydrazone, naltrexone, narceine, nicomorphine, norlevorphanol, normethadone, normorphine, norpipanone, opium, oxycodone, oxymorphone, papaveretum, papaverine, pentazocine, phenadoxone, phenazocine, phenoperidine, piminodine, piritramide, proheptazine, promedol, propiram, propoxyphene, remifentanyl, spiradoline, sufentanyl, tilidine, U50,488, and U69,593, amiphenazole, cyclazocine, levallorphan, nalmeferine, nalorphine, naloxone, and naltrexone or pharmaceutically-acceptable salts thereof, or mixtures thereof.

Examples of peptide opioids include, but are not limited to, Tyr-Gly-Gly-Phe-Leu ([Leu⁵]enkephalin), Tyr-Gly-Gly-Phe-Met ([Met⁵]enkephalin), Tyr-Gly-Gly-Phe-Leu-Arg-Arg-Ile-Arg-Pro-Lys-Leu-Lys-Trp-Asp-Asn-Gln (DynorphinA), Tyr-Gly-Gly-Phe-Leu-Arg-Arg-Gln-Phe-Lys-Val-Val-Thr (Dynorphin B), Tyr-Gly-Gly-Phe-Leu-Arg-Lys-Tyr-Pro-Lys (α -Neoendorphin), Tyr-Gly-Gly-Phe-Leu-Arg-Lys-Tyr-Pro (β -Neoendorphin), Tyr-Gly-Gly-Phe-Met-Thr-Ser-Glu-Lys-Ser-Gln-Thr-Pro-Leu-Val-Thr-Leu-Phe-Lys-Asn-Ala-Ile-Ile-Lys-Asn-Ala-Tyr-Lys-Lys-Gly-Glu (β _h-Endorphin), [D-Ala²,MePhe⁴Gly(ol)⁵]enkephalin (DAMGO), [D-Pen²,D-Pen⁵]enkephalin (DPDPE), [D-Ser²,Leu⁵]enkephalin-Thr⁶ (DSLET), [D-Ala²,D-Leu⁵]enkephalin (DADL), D-Phe-Cys-Tyr-D-Trp-Orn-Thr-Pen-Thr-NH₂ (CTOP), [D-Ala²,N-MePhe⁴,Met(O)⁵-ol]enkephalin (FK-33824), Tyr-D-Ala-Phe-Asp-Val-Val-Gly-NH₂ ([D-Ala²]Deltorphin I), Tyr-D-Ala-Phe-Glu-Val-Val-Gly-NH₂ ([D-Ala²Glu⁴]Deltorphin (Deltorphin II)), Tyr-Pro-Phe-Pro-NH₂

(Morphiceptin), Tyr-Pro-MePhe-D-Pro-NH² (PL-017), [D-Ala²,Leu⁵,Cys⁶]enkephalin (DALCE) or pharmaceutically-acceptable salts thereof, or mixtures thereof. Preferred opioids include morphine, loperamide and loperamide derivatives such as those disclosed in United States Patent Nos. 5,763,445; 5,981,513; 5,869,521; 5,744,458; 5,760,023; 5,798,093; 5,849,762; 5,811,078; 6,004,964; 5,962,477; 5,688,955; 5,888,494; 5,646,151; and 5,667,773 (all of which patents are incorporated by reference herein), or
5 pharmaceutically-acceptable salts thereof, or mixtures thereof. The most preferred opioid is morphine or a pharmaceutically-acceptable salt thereof.

As used herein, the term "local anesthetic" means any drug that provides local numbness or analgesia or any drug that provides a regional blockage of nociceptive pathways (afferent and/or efferent) and that is not an agonist or an antagonist of an opioid
10 receptors. The local anesthetic can be any local anesthetic known or to be developed. Examples of local anesthetics suitable for use with the invention include: ambucaine, amolanone, amylcaine, benoxinate, benzocaine, betoxycaine, biphenamine, bupivacaine, butacaine, butamben, butanilcaine, butethamine, butoxycaine, carticaine, chloroprocaine, cocaethylene, cocaine, cyclomethycaine, dibucaine, dimethisoquin, dimethocaine,
15 diperodon, dyclonine, ecogonidine, ecogonine, euprocine, fenalcomine, formocaine, hexylcaine, hydroxytetracaine, isobutyl *p*-aminobenzoate, leucinocaine, levaxadol, lidocaine, mepivacaine, meprylcaine, metabutoxycaine, methyl chloride, myrtecaine, naepaine, octacaine, orthocaine, oxethazaine, parenthoxycaine, phenacaine, phenol, piperocaine, piridocaine, polidocanol, pramoxine, prilocaine, procaine, propanocaine,
20 proparacaine, propipocaine, propoxycaine, pseudococaine, pyrrocaine, ropivacaine, salicyl alcohol, tetracaine, tolycaine, trimecaine, zolamine, or pharmaceutically-acceptable salts thereof, or mixtures thereof.

The amide and ester type local anesthetics are preferred. Amide type local anesthetics are characterized by an amide functionality, while ester type local anesthetics
25 contain an ester functionality. Preferred amide type local anesthetics, include lidocaine, bupivacaine, prilocaine, mepivacaine, etidocaine, ropivacaine, dibucaine, and pharmaceutically-acceptable salts thereof and mixtures thereof. Preferred ester type local anesthetics include tetracaine, procaine, benzocaine, chloroprocaine, and pharmaceutically-acceptable salts thereof and mixtures thereof. The most preferred local anesthetic is
30 lidocaine. The meaning of "local anesthetic" also encompasses drugs not traditionally associated with local anesthetic properties but which have a local-anesthetic effect, for example, non-narcotic analgesics, such as, acetylsalicylic acid, ketoprofen, piroxicam, diclofenac, indomethacin, ketorolac, Vioxx®, and Celebrex®. Furthermore, in order to
35 improve the effectiveness and tolerance of the present topically-effective therapy, local anesthetics with different pharmacodynamics and pharmacokinetics may be combined in a

composition of the invention. A preferred combination of local anesthetics is lidocaine and prilocaine and another preferred combination is lidocaine and tetracaine.

As used herein, the term "local delivery" of a therapeutic, means topical application of the therapeutic to a subject, whereafter a therapeutically-effective amount of the therapeutic is absorbed in the immediate application area, preferably, without significant absorption into the blood stream.

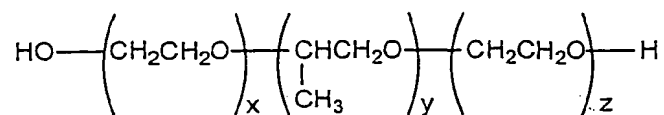
As used herein, a "therapeutically-effective amount" of the compositions of the invention means the amount required to induce a local-anesthetic effect or numbness sufficient to ameliorate pain induced by ulceration, inflammation, or lesions of the buccal or nasal membrane or other mucous membranes or the pain associated with mucosal trauma, such as dental surgery. Preferably, the active agents of the composition are not absorbed systemically.

As used herein, the term "subject" means any animal, preferably a mammal, more preferably a human.

As used herein the term "mucoadhesive" means a natural or synthetic substance, e.g., gels, pastes, macromolecules, polymers, and oligomers, or mixtures thereof, that can adhere to a subject's mucous membrane for a period of time sufficient to locally deliver a therapeutically-effective amount of a composition of the invention to a subject. Adhesion of mucoadhesives to the mucous membrane occurs primarily via secondary chemical bonds, such as hydrogen bonding and Van der Waal forces (Tabor *et al.*, 1977 *J. Colloid Interface Sci.* 58:2 and Good 1977 *J. Colloid Interface Sci.* 59:398). Mucoadhesive substances often form viscous aqueous solutions. The composition itself does not need to be mucoadhesive, as long as it can form a mucoadhesive gel upon on the contact with the mucous membrane. For example, gellan gum itself is a very weak mucoadhesive. On contact with the buccal membrane, gellan gum can interact with the ions in the mucous membrane and form an adhesive gel layer. According to the invention, mucoadhesives possess binding properties that may be distinguished from non-mucoadhesives by comparing the degree of adhesion to a mucosal surface. For example, comparison of a potential mucoadhesive with a control emulsion of comparable viscosity prepared without mucoadhesive properties, e.g., a starch solution. At similar viscosities, the emulsion prepared with the mucoadhesive will bind to the mucosal surface more strongly than will the control emulsion, preferably at least 25% greater mucosal binding than the control emulsion, more preferably at least 50% greater, still more preferably at least 100% greater mucosal binding. Either mechanical binding to mucous membrane *per se* or the degree of biological effect of a drug delivered may be used as a measurement parameter for mucoadhesion. This test may be used to distinguish preferred mucoadhesives. Substances can be screened for their ability to be used as mucoadhesives for local delivery of compositions of the invention according to the methodology described in Smart *et al.*, 1982 *J. Pharm. Pharmacol.* 34:70P and Smart *et al.*,

1984 *J. Pharm. Pharmacol.* 36:295, which methodology comprises estimating values of adhesive strength between the substance and the mucous membrane. Preferably, the mucoadhesive is water soluble, such that at least 1% by weight of the mucoadhesive is soluble in water at 25 °C. In a preferred embodiment, the mucoadhesive will exhibit non-Newtonian fluid properties, *i.e.*, the viscosity decreases with increasing shear forces. Accordingly, the viscosity of the composition can be modulated by altering the shear forces present when the composition is applied to a surface. A composition with non-Newtonian fluid properties, becomes less viscous when shaken or atomized, then, upon standing, returns to its original viscosity.

Examples of mucoadhesives for use in the present invention include, but are not limited to, pectin, alginic acid, chitosan, hyaluronic acid, polysorbates, such as polysorbate-20, -21, -40, -60, -61, -65, -80, -81, -85; poly(ethyleneglycol), such as PEG-7, -14, -16, -18, -55, -90, -100, -135, -180, -4, -240, -6, -8, -9, -10, -12, -20, or -32; oligosaccharides and polysaccharides, such as gellan, carrageenan, xanthan gum, gum Arabic, and dextran; cellulose esters and cellulose ethers; modified cellulose polymers, such as carboxymethylcellulose, hydroxyethylcellulose, hydroxypropyl methylcellulose, hydroxyethyl ethylcellulose; polyether polymers and oligomers, such as polyoxyethylene; condensation products of poly(ethyleneoxide) with various reactive hydrogen containing compounds having long hydrophobic chains (*e.g.* aliphatic chains of about 12 to 20 carbon atoms), for example, condensation products of poly(ethylene oxide) with fatty acids, fatty alcohols, fatty amides, polyhydric alcohols; polyether compounds, such as poly(methyl vinyl ether), polyoxypropylene of less than 10 repeating units; polyether compounds, such as block copolymers of ethylene oxide and propylene oxide; mixtures of block copolymers of ethylene oxide and propylene oxide with other excipients, for example, pluronic lethicin organogel (*see* 1997 *International Journal of Pharmaceutical Compounding* 1:71); poly(vinyl alcohol); polyacrylamide; hydrolyzed polyacrylamide; poly(vinyl pyrrolidone); poly(methacrylic acid); poly(acrylic acid) or crosslinked polyacrylic acid, such as carbomer, *i.e.*, a homopolymer of acrylic acid crosslinked with either an allyl ether of pentaerythritol, an allyl ether of sucrose, or an allyl ether of propylene (*e.g.*, Acrisint® 400, 410, or 430 commercially available from 3V Inc. Weehawkin, NJ); Orabase® (*i.e.*, a mixture of gelatine, pectin and sodium carboxymethyl cellulose in a plasticized hydrocarbon gel, commercially available from Hoyt laboratories, Needham, MA); Carafate® (sulfated sucrose and aluminum hydroxide, commercially available from Marion Laboratories, Inc., Kansas City, MO). The block copolymers of ethylene oxide and propylene oxide are particularly preferred. Preferred block copolymers of ethylene oxide and propylene oxide are represented by formula I below:



I

5 Wherein x is an integer having an average value within the range of from about 2 to about 128; y is an integer having an average value within the range of from about 14 to about 80; and z is an integer having an average value within the range of from about 2 to about 128. Preferably, x and y are about equal. More preferred block copolymers of ethylene oxide and propylene oxide, falling within the genus represented by formula I, are shown in Table
10 1 below.

15

20

25

30

35

TABLE 1

	Name	Trade Name	approximate value of x	approximate value of y	approximate value of z
	Poloxamer 101	Pluronic® L-31	2	16	2
5	Poloxamer 105	Pluronic L-35	11	16	11
	Poloxamer 108	Pluronic F-38	46	16	46
	Poloxamer 122	Calgene Nonionic® 1042-L	5	21	5
	Poloxamer 123	Pluronic L-43	7	21	7
	Poloxamer 124	Pluronic L-44	11	21	11
10	Poloxamer 181	Pluronic L-61	3	30	3
	Poloxamer 182	Pluronic L-62	8	30	8
	Poloxamer 183	Calgene Nonionic 1063-L	10	30	10
	Poloxamer 184	Pluronic L-64	13	30	13
15	Poloxamer 185	Pluronic P-65	19	30	19
	Poloxamer 188	Pluronic F-68	75	30	75
	Poloxamer 212	Calgene Nonionic 1072-L	8	35	8
	Poloxamer 215	Calgene Nonionic 1075-P	24	35	24
	Poloxamer 217	Pluronic F-77	52	35	52
20	Poloxamer 231	Pluronic L-81	6	39	6
	Poloxamer 234	Pluronic P-84	22	39	22
	Poloxamer 235	Pluronic P-85	27	39	27
	Poloxamer 237	Pluronic F-87	62	39	62
25	Poloxamer 238	Pluronic F-88	97	39	97
	Poloxamer 282	Pluronic L-92	10	47	10
	Poloxamer 284	Calgene Nonionic 1094-P	21	47	21
	Poloxamer 288	Pluronic F-98	122	47	122
	Poloxamer 331	Pluronic L-101	7	54	7
30	Poloxamer 333	Pluronic P-103	20	54	20
	Poloxamer 334	Pluronic P-104	31	54	31
	Poloxamer 335	Pluronic P-105	38	54	38

35

TABLE 1 (Cont.)

Name	Trade Name	approximate value of x	approximate value of y	approximate value of z
Poloxamer 338	Pluronic F-108	128	54	128
5 Poloxamer 401	Pluronic L-121	6	67	6
Poloxamer 403	Pluronic P-123	21	67	21
Poloxamer 407	Pluronic F-127	98	67	98

The most preferred mucoadhesive for use with the invention is poloxamer 407. The
 10 block copolymers of ethylene oxide and propylene oxide sold under the trade name Pluronic
 are commercially available, *e.g.*, BASF (Washington, NJ). The block copolymers of
 ethylene oxide and propylene oxide sold under the trade name Calgene are commercially
 available, *e.g.*, Calgene Chemical, Inc. Skokie, IL.

Preferably, when administered to a subject, the compositions of the invention are
 15 sterile.

Suitable preservatives include, but are not limited to, quaternary ammonium
 compounds, such as benzalkonium chloride, benzethonium chloride, cetrimide, dequalinium
 chloride, and cetylpyridinium chloride; mercurial agents, such as phenylmercuric nitrate,
 phenylmercuric acetate, and thimerosal; alcoholic agents, for example, chlorobutanol,
 20 phenylethyl alcohol, and benzyl alcohol; antibacterial esters, for example, esters of
 para-hydroxybenzoic acid; and other anti-microbial agents such as chlorhexidine,
 chlorocresol, and polymyxin.

Suitable chelating agents include, but are not limited to, deferoxamine, ditiocarb
 sodium, edetate calcium disodium, edetate disodium, edetate sodium, edetate trisodium,
 25 penicillamine, pentetate calcium trisodium, pentetic acid, succimer, trientin.

Preferably, the pH of the composition is within the range of from about 2 to about 9,
 more preferably, about 3 to about 7, even more preferably about 4 to about 5, and optimally
 about 4.5. Under acidic conditions, protonation permits H-bonding between the polymer
 and the mucin network, resulting in enhanced retention of the polymer in contact with a
 30 mucosal surface. The pH can be adjusted by adding an aqueous acid or base, dropwise to
 the composition until the desired pH is obtained. Any physiologically acceptable pH
 adjusting acids, bases or buffers are acceptable, *e.g.*, acids, such as acetic, boric, citric,
 lactic, phosphoric, hydrochloric; bases, such as sodium hydroxide, sodium phosphate,
 sodium borate, sodium citrate, sodium acetate, sodium lactate, THAM
 35 (trishydroxymethylaminomethane); and buffers such as citrate/dextrose, sodium
 bicarbonate, ammonium chloride and mixtures thereof, preferably, 0.1 normal hydrochloric

acid for a pH of less than 7 and 0.1 normal aqueous sodium hydroxide for a pH of greater than 7.

The composition of the invention can also comprise NMDA receptor antagonists including, but not limited to, dextromethorphan, dextrophan, ketamine, pyroloquinolin quinone, *cis*-4-(phosphonomethyl)-2-piperidine carboxylic acid, MK801, memantine, D-methadone, or pharmaceutically-acceptable salts thereof.

The compositions of the invention can also include other excipients and pharmaceuticals. Examples of excipients that can be included in the topical compositions of the invention include, but are not limited to, antibiotics, analgesics, antifungal agents, non-steroidal anti-inflammatory agents, anti-tussive agents, expectorants, glucocorticoids, vitamins, anti-oxidants, flavoring agents, sweetening agents, iso-osmotic agents, moisturizers, emollients, buffering agents, solubilizing agents, penetration agents, protectants, surfactants, and propellants, and other conventional systemic or topical pain relief therapies, analgesics, and pharmaceuticals.

Examples of suitable antibiotics include, but are not limited to, aminoglycoside antibiotics; such as apramycin, arbekacin, bambarmycins, butirosin, dibekacin, neomycin, neomycin undecylenate, netilmicin, paromomycin, ribostamycin, sisomicin, and spectinomycin; amphenicol antibiotics, such as azidamfenicol, chloramphenicol, florfenicol, and thiamphenicol; ansamycin antibiotics, such as rifamide and rifampin; carbacephems, such as loracarbef; carbapenems, such as biapenem and imipenem; cephalosporins, such as cefaclor, cefadroxil, cefamandole, cefatrizine, cefazedone, cefozopran, cefpimizole, cefpiramide, and cefpirome; cephamycins, such as cefbuperazone, cefmetazole, cefminox; monobactams, such as aztreonam, carumonam, and tigemonam; oxacephems, such as flomoxef, and moxalactam; penicillins, such as amdinocillin, amdinocillin pivoxil, amoxicillin, bacampicillin, benzylpenicillinic acid, benzylpenicillin sodium, epicillin, fenbenicillin, floxacillin, penamccillin, penethamate hydriodide, penicillin *o*-benethamine, penicillin O, penicillin V, penicillin V benzathine, penicillin V hydrabamine, penimepicycline, and phencihicillin potassium; lincosamides, such as clindamycin, and lincomycin; macrolides, such as azithromycin, carbomycin, clarithromycin, dirithromycin, erythromycin, erythromycin acistrate; polypeptides, such as amphomycin, bacitracin, capreomycin, colistin, enduracidin, and enviomycin; tetracyclines, such as apicycline, chlortetracycline, clomocycline, and demeclocycline; 2,4-diaminopyrimidines, such as brodimoprim; nitrofurans, such as furaltadone, and furazolum chloride; quinolones and analogs, such as cinoxacin, ciprofloxacin, clinafloxacin, flumequine, and grepagloxacin; sulfonamides, such as acetyl sulfamethoxypyrazine, benzylsulfamide, noprlylsulfamide, phthalylsulfacetamide, sulfachrysoidine, and sulfacytine; sulfones, such as diathymosulfone, glucosulfone sodium, and solasulfone; and others, such as cycloserine, mupirocin, tuberin.

Examples of suitable analgesics include, but are not limited to, aceclofenac, acetaminophen, acetaminosalol, acetanilide, acetylsalicylsalicylic acid, alclofenac, alminoprofen, aloxiprin, aluminum bis(acetylsalicylate), aminochlorthenoxazin, 2-amino-4-picoline, aminopropylon, aminopyrine, ammonium salicylate, amtolmetin guacil, antipyrine, antipyrine salicylate, antrafenine, apazone, aspirin, benorylate, benoxaprofen, benzpiperylon, benzydamine, bermoprofen, bromfenac, p-bromoacetanilide, 5-bromosalicylic acid acetate, bucerin, bufexamac, bumadizon, butacatin, calcium acetylsalicylate, carbamazepine, carbiphen, carsalam, chlorthenoxazin(e), choline salicylate, cinchophen, cirmadol, clometacin, clonixin, cropropamide, crotethamide, dexoadrol difenamizole, difunisal, dihydroxyaluminum acetylsalicylate, dipyrone, dipyrone, emorfazone, enfenamic acid, eprizole, etersalate, ethenzamide, ethoxazene, etodolac, felbinac, fenoprofen, floctafenine, flufenamic acid, fluorenone, flupirtine, fluproquazone, flurbiprofen, fosfosal, gentisic acid, glafenine, ibufenac, imidazole salicylate, indomethacin, indoprofen, isofezolac, isoladol, isonixin, ketoprofen, ketorolac, p-lactophenolide, lefetamine, lornoxicam, loxoprofen, lysine acetylsalicylate, magnesium acetylsalicylate, methotrimoprazine, metofoline, mofezolac, morazone, morpholine salicylate naproxen, nefopam, nifenazone, 5'-nitro-2'-propoxyacetanilide, parsalimide, perisoxal, phenacetin, phenazopyridine hydrochloride, phenocoll, phenopyrazone, phenyl acetylsalicylate, phenyl salicylate, phenylamidol, pipebuzone, piperylon, propacetamol, propyphenazone, ramifenazone, rimazolium metilsulfate, salacetamide, salicin, salicylamide, salicylamide o-acetic acid, salicylsulfuric acid, salsalate, salverine, simetride, sodium salicylate, suprofen, talniflumate, tenoxicam, terofenamate, tetrandrine, tinoridine, tolfenamic acid, tramadol, tropesin, viminol, xenbucin, and zomepirac.

Examples of suitable antifungal agents include, but are not limited to, polyenes, such as amphotericin b, candicidin, mepartricin, natamycin, and nystatin; allylamines, such as butenafine, and naftifine; imidazoles, such as bifonazole, butoconazole, chlordanol, flutrimazole, isoconazole, ketoconazole, and lanoconazole; thiocarbamates, such as tolclate, tolindate, and tolinaftate; triazoles, such as fluconazole, itraconazole, saperconazole, and terconazole; and others, such as bromosalicylchloranilide, buclosamide, calcium propionate, chlorphenesin, and ciclopirox; and others, such as azaserine, griseofulvin, oligomycins, neomycin undecylenate, pyrrolnitrin, siccanin, tubercidin, viridin.

Examples of suitable non-steroidal anti-inflammatory agents include, but are not limited to, aminoarylcarboxylic acid derivatives, such as enfenamic acid, etofenamate, flufenamic acid, isonixin, meclofenamic acid, mefenamic acid, niflumic acid, talniflumate, terofenamate, and tolfenamic acid; arylacetic acid derivatives, such as aceclofenac, acemetacin, alclofenac, amfenac, amtolmetin guacil, bromfenac, bufexamac, cinmetacin, clopirac, diclofenac sodium, etodolac, felbinac, fenclozic acid, fentiazac, glucametacin,

ibufenac, indomethacin, isofezolac isoxepac, lonazolac, metiazinic acid, mofezolac, oxametacine, pirazolac, proglumetacin, sulindac, tiaramide, tolmetin, tropesin, and zomepirac; arylbutyric acid derivatives, such as bumadizon, butibufen, fenbufen, xenbucin; arylcarboxylic acids, such as clidanac, ketorolac, tinoridine; arylpropionic acid derivatives, such as alminoprofen, benoxaprofen, bermoprofen, bucloxic acid, carprofen, fenoprofen, flunoxaprofen, flurbiprofen, ibuprofen, ibuproxam, indoprofen, ketoprofen, loxoprofen, naproxen, oxaprozin, piketoprofen, pirprofen, pranoprofen, protizinic acid, suprofen, tiaprofenic acid, ximoprofen, and zaltoprofen; pyrazoles, such as difenamizole, and epirozole; pyrazolones, such as apazone, benzpiperylon, feprazone, mofebutazone, morazone, oxyphenbutazone, phenylbutazone, pipebuzone, propyphenazone, ramifenazone, suxibuzone, and thiazolinobutazone; salicylic acid derivatives, such as acetaminosalol, aspirin, benorylate, bromosaligenin, calcium acetylsalicylate, diflunisal, etersalate, fendosal, gentisic acid, glycol salicylate, imidazole salicylate, lysine acetylsalicylate, mesalamine, morpholine salicylate, 1-naphtyl salicylate, olsalazine, parsalmide, phenyl acetylsalicylate, phenyl salicylate, salacetamide, salicylamide *o*-acetic acid, salicylsulfuric acid, salsalate, sulfasalazine; thiazinecarboxamides, such as ampiroxicam, droxicam, isoxicam, lornoxicam, piroxicam, and tenoxicam; and others, such as ϵ -acetamidocaproic acid, *s*-adenosylmethionine, 3-amino-4-hydroxybutyric acid, amixetrine, bendazac, benzydamine, α -bisabolol, bucololome, difenpiramide, ditazol, emorfazone, fepradinol, guaiazulene, nabumetone, nimesulide, oxaceprol, paranyline, perisoxal, proquazone, superoxide dismutase, tenidap, and zilenton.

Examples of suitable antitussive agents include, but are not limited to, alloclamide, amicibone, benproperine, benzonatate, bibenzonium bromide, bromoform, butamirate, butethamate, caramiphen ethanedisulfonate, carbetapentane, chlrophedianol, clobutinol, clopefastine, codeine, codeine methyl bromide, codeine *n*-oxide, codeine phosphate, codeine sulfate, cyclexanone, dimethoxanate, dropropizine, drotebanol, eprazinone, ethyl dibunate, ethylmorphine, fominoben, guaiaipate, hydrocodone, isoaminile, levopropoxyphene, morclofone, narceine, mormethadone, noscapine, oxeladin, oxolamine, pholcodine, picoperine, pipazethate, piperidione, prenoxdiazine hydrochloride, racemethorphan, sodium dibunate, tipepidine, and zipeprol.

Example of suitable expectorants include, but are not limited to, ambroxol, ammonium bicarbonate, ammonium carbonate, bromhexine, calcium iodide, carbocysteine, guaiacol, guaiacol benzoate, guaiacolcarbonate, guaiacol phosphate, guaifenesin, guaithylline, hydriodic acid, iodinated glycerol, potassium guaiacolsulfonate, potassium iodide, sodium citrate, sodium iodide, storax, terebene, terpin, and trifolium.

Suitable glucocorticoids include, but are not limited to, 21-acetoxypregnenolone, alclometasone, algestone, amcinonide, beclomethasone, betamethasone, budesonide, chloroprednisone, clobetasol, clobetasone, clocortolone, cloprednol, corticosterone,

cortisone, cortivazol, deflazacort, desonide, desoximetasone, dexamethasone, diflorasone, diflucortolone, difluprednate, enoxolone, fluazacort, flucoronide, flumethasone, flunisolide, fluocinolone acetonide, fluocinonide, flucortin butyl, fluocortolone, fluorometholone, fluperolone acetate, fluprednidene acetate, fluprednisolone, flurandrenolide, fluticasone propionate, formocortal, halcinonide, halobetasol propionate, halometasone, halopredone acetate, hydrocortamate, hydrocortisone, loteprednol etabonate, mazipredone, medrysone, meprednisone, methylprednisolone, mometasone furoate, paramethasone, prednicarbate, prednisolone, prednisolone 25-diethylamino-acetate, prednisolone sodium phosphate, prednisone, prednival, prednylidene, rimexolone, tixocortol, triamcinolone, triamcinolone acetonide, triamcinolone benetonide, and triamcinolone hexacetonide.

Suitable vitamins include, but are not limited to calcipotriene, calcitriol, ergosterol, 1 α -hydroxycholecalciferol, vitamin D₂, vitamin D₃, ascorbic acid, calcium ascorbate, nicotinamide ascorbate, sodium ascorbate, α -carotene, β -carotene, δ -carotene, vitamin A, cobamamide, folic acid, hydroxocobalamin, sodium folate, vitamin B₁₂, menadiol, menadione, menadoxime, menaquinones, phylloquinone, vitamin K₃, inositol, β -tocopherol, γ -tocopherol, δ -tocopherol, vitamin E, vitamin E acetate, and vitamin U.

Examples of suitable anti-oxidants include, but are not limited to, ascorbic acid, sodium ascorbate, sodium bisulfite, sodium thiosulfate, 8-hydroxy quinoline, and *N*-acetyl cysteine.

Examples of suitable flavoring agents include, but are not limited to, oil of spearmint, peppermint, wintergreen, sassafras, clove, sage, eucalyptus, marjoram, cinnamon, lemon, and orange, and methyl salicylate.

Examples of suitable sweetening agents include, but not limited to, sucrose, lactose, maltose, sorbitol, xylitol, sodium cyclamate, perillartine, AMP (aspartyl phenyl alanine, methyl ester), and saccharine.

The compositions of the present invention optionally can include an iso-osmotic agent which functions to prevent irritation of the mucosa by the composition. Examples of pharmaceutically-acceptable iso-osmotic agents which can be used include sodium chloride, dextrose, and calcium chloride.

Preferably, the amount of local anesthetic in the composition is within the range of from about 0.005 percent to about 2 percent of the total weight of the composition, more preferably, of from about 0.01 percent to about 0.5 percent of the total weight of the composition.

For treatment of oral mucositis, a preferred concentration of local anesthetic is from about 0.02 percent to about 0.1 percent of the total weight of the composition, more preferably, about 0.04 percent to about 0.08 percent. For treatment of more painful conditions, such as dental surgery (*e.g.*, tooth extraction or root canal), a preferred

concentration of local anesthetic is from about 0.1 percent to about 0.4 percent of the total weight of the composition, more preferably, about 0.2 percent to about 0.3 percent.

Preferably, the amount of opioid in the composition is within the range of from about 0.005 percent to about 3 percent of the total weight of the composition, more preferably, of from about 0.01 percent to about 2 percent, still more preferably, of from about 0.05 percent to about 1 percent of the total weight of the composition. For treatment
5 of oral mucositis, a preferred concentration of opioid is from about 0.1 percent to about 0.3 percent of the total weight of the composition. For treatment of more painful conditions, such as dental surgery, a preferred concentration of opioid is from about 0.3 percent to about 0.8 percent of the total weight of the composition, more preferably, about 0.4 percent to about 0.5 percent.

10 Preferably, the amount of mucoadhesive in the composition is within the range of from about 0.1 percent to about 40 percent of the total weight of the composition, more preferably, of from about 10 percent to about 30 percent, and optimally, of from about 15 percent to about 25 percent of the total weight of the composition.

15 Preferably, the amount of water in the composition is within the range of from about 95 percent to about 10 percent of the total weight of the composition, more preferably, of from about 90 percent to about 50 percent, and optimally, of from about 85 percent to about 75 percent of the total weight of the composition.

20 When a chelating agent is used, preferably, it is present in an amount within the range of from about 0.005 percent to about 1 percent of the total weight of the composition, more preferably, of from about 0.01 percent to about 0.5 percent, still more preferably, of from about 0.05 percent to about 0.2 percent of the composition.

25 When a preservative is used, preferably, it is present in an amount within the range of from about 0.0001 percent to about 0.2 percent of the total weight of the composition, more preferably, of from about 0.0005 percent to about 0.1 percent, and optimally, of from about 0.001 percent to about 0.05 percent of the total weight of the composition.

To relieve pain from mucositis, the compositions or the invention are topically applied directly to the affected area. The compositions of the invention can be applied to the affected area of the mucous membrane in any conventional manner well known in the art, for example, as a mist via an aerosol applicator, by cannula, via a patch, by a dropper, or
30 by an applicator stick, preferably as a mist, more preferably as a metered-dose mist. A mist can be sprayed onto the area to be treated via an aerosol container, pressurized or non-pressurized, preferably a non-pressurized pump. For more specific applications, a cannula can be used. The cannula can be attached to a pressurized or non-pressurized pump, preferably a non-pressurized pump.
35

A suitable non-pressurized pump for application of compositions of the invention can comprise a container, a valve, an actuator, and optionally a dip tube. The non-

pressurized pump's container can be metal, such as a tin plated steel or aluminum, glass, or plastic. The valve's primary purpose is to regulate the flow of product from the container. It provides a means of discharging the desired amount. Suitable spray valves are described in *Remington's Pharmaceutical Sciences* 18th Edition, ed. Alfonso Gennaro, Mack Publishing Co. Easton, PA, 1990 pp. 1703-1704, incorporated herein by reference. The actuator provides a means for releasing the contents from a pressurized container. Suitable actuators are described in *Remington's Pharmaceutical Sciences* 18th Edition, ed. Alfonso Gennaro, Mack Publishing Co. Easton, PA, 1990 pp. 1704-1705, incorporated herein by reference.

Preferably, the metered pump is a VP 7 Screw-On Pump (90 μ l, 18/415) commercially available from Valois of America, Inc. (Greenwich, CT). The VP 7 screw-on pump is manufactured from polyethylene and polypropylene. It is designed in a way such that the hydraulically opening clapper eliminates the use of any elastomeric gaskets in contact with the product. The pump has an annular dosing chamber, which fills only at the full return of the actuator to ensure full dosing and precision.

The preferred actuator is the 132C-BL GP4 BL long throat actuator commercially available from Valois Pharmaceuticals, Inc. Preferably, the actuator is manufactured from polyethylene and polypropylene and, preferably, contains a captive insert to provide a well-atomized spray pattern. The captive insert also reduces the dead volume in the actuator.

When a cannula is used, for application to a specific area rather than as a spray, the preferred actuator is a stainless-steel cannula of about 73 mm in length, for example, the 215 stainless-steel cannula commercially available from Valois Pharmaceuticals, Inc. Polyethylene or polypropylene cannulas can also be used.

The compositions of the invention can also be delivered to the buccal or nasal cavity via a patch that is applied adjacent to the area of skin to be treated. As used herein a "patch" comprises at least a composition of the invention and a covering layer, such that, the patch can be placed over the area to be treated. Preferably, the patch is designed to maximize local delivery and to minimize absorption into the circulatory system, reduce lag time, promote uniform absorption, and reduce mechanical rub-off. Suitable patches are described in *Transdermal and Topical Drug Delivery Systems*, Interpharm Press, Inc. p. 249-297, incorporated herein by reference. Suitable patches for buccal delivery of compositions of the invention is disclosed in United States Patent Nos. 5,713,852 and 4,900,552, both of which are incorporated herein by reference.

The amount of the composition of the invention applied to the buccal or nasal passages will vary depending on the particular mucoadhesive, local anesthetic, and opioid used; the nature and severity of the mucosal lesion or inflammation being treated, and the subject. The composition should be applied to the affected area as recommended by a physician, preferably, as needed by the patient to relieve pain. For example, a dose of about

0.05 mg to about 4 mg morphine sulfate and 0.02 mg to about 3 mg of lidocaine hydrochloride in about 0.5g to about 3 g of composition can be delivered to the affected area. When applying as a spray, a dose of about 2 mg morphine sulfate and about 1 mg lidocaine hydrochloride in about 1.5 g of composition can be delivered to the affected area. For more precise applications by cannula, a dose of about 2 mg morphine sulfate and about 1 mg lidocaine hydrochloride in about 0.4 g of composition can be delivered to the affected area.

In a preferred embodiment of administration, the dose is delivered with a spray actuator in about 8 to about 20 separate spray shots, more preferably about 16 spray shots, wherein each spray shot weighs about 50 mg to about 150 mg, more preferably about 100 mg. In another preferred embodiment of administration, the dose is delivered via cannula in about 4 spray shots, wherein each spray shot weighs about 100 mg.

Although the present invention has been described in considerable detail with reference to certain preferred embodiments, other embodiments are possible. Therefore, the spirit and scope of the appended claims should not be limited to the description of the preferred embodiments contained herein.

EXAMPLES

The following examples are provided for illustrative purposes only and are not to be construed as limiting the invention's scope in any manner.

EXAMPLE 1

A composition of the present invention is described in Table 2 below.

5

10

15

Ingredient	Weight	Weight percent
Morphine sulfate pentahydrate	122.6 mg	0.2
Lidocaine hydrochloride monohydrate	65.4 mg	0.06
Poloxamer 407	20 g	19.3
Edetate disodium dihydrate	100 mg	0.1
Benzalkonium chloride (50% aqueous solution)	30 mg	0.03
Sterile water	80 g	77.4
0.1 N aqueous hydrochloric acid	3 g	2.9

20

25

30

35

Morphine sulfate pentahydrate (122.6 mg), lidocaine (65.4 mg) hydrochloride monohydrate, and edetate disodium dihydrate (100 mg) were dissolved in 80 g of sterile water. The resulting solution was cooled to 10°C in an ice bath and poloxmer 407 (20g) was slowly added with mixing until the Poloxmer 407 completely dissolved. The solution was maintained at about 10°C until the foam collapsed. About 4 g of the solution was added to a 5 ml vial and a Valois VP7/90 18/415 pump was screwed onto the vial and refrigerated at 4°C for 30 minutes. The vial was removed from the refrigerator and the metered pump was primed using the Valois 165 actuator. The Valois 165 actuator was removed and the filled vial was stored at 4°C until the foam collapsed. The vial was removed from the refrigerator and kept at room temperature (25°C) until the contents gelled.

The viscosity of the above-prepared oral spray was measure using a Brookfield RVT viscometer. At 30°C the viscosity was 82,666 cps (averaged over three determinations) and at 40°C the viscosity was 95,666 cps (averaged over three determinations).

The composition can be applied as follows. Attach the long throat actuator to the metering pump and store the unit at 4°C for at least 30 minutes. To prime the pump (7-8 sprays), with actuator in the up position, press the actuator firmly and quickly to spray into a waste container, hold the actuator for about one second when it is in the pressed position following each spray. With actuator in the up position, press the actuator firmly and quickly to spray onto the surface of the subject to be treated. Hold the actuator for two to three seconds when it is in the pressed position following each spray. Apply a total of 16

spray shots of for a total application of about 2 mg morphine sulfate and about 1 mg lidocaine hydrochloride in about 1.5 g of composition. Once the spray makes contact with the mucous membrane at body temperature, the liquid will form a viscous mucoadhesive gel. If it takes more than 90 seconds to apply 16 spray shots, store the unit at 4°C for 10 minutes to cool the content before further usage.

5

EXAMPLE 2

A second composition of the present invention is described in Table 2 below.

	Ingredient	Weight	Weight percent
10	Morphine sulfate pentahydrate	490.5 mg	0.48%
	Lidocaine hydrochloride monohydrate	261.5 mg	0.25%
	Poloxamer 407	20 g	19.4%
	Edetate disodium dihydrate	100 mg	0.097
15	Benzalkonium chloride (50% aqueous solution)	30 mg	0.029%
	Sterile water	80 g	77.6%
	0.05 N aqueous hydrochloric acid	2.2 g	2.1%

20 Morphine sulfate pentahydrate (490.48 mg), lidocaine (261.6 mg) hydrochloride monohydrate, and edetate disodium dihydrate (100 mg) were dissolved in 80 g of sterile water. The resulting solution was cooled to 10°C in an ice bath and poloxmer 407 (20g) was slowly added with mixing until the Poloxmer 407 completely dissolved. The solution was maintained at about 10°C until the foam collapsed. About 4 g of the solution was added to a 5 ml vial and a Valois VP7/90 18/415 pump was screwed onto the vial and
25 refrigerated at 4°C for 30 minutes. The vial was removed from the refrigerator and the metered pump was primed using the Valois 165 actuator. The Valois 165 actuator was removed and the filled vial was stored at 4°C until the foam collapsed. The vial was removed from the refrigerator and kept at room temperature (25°C) until the contents gelled.

30 The viscosity of the above-prepared oral spray was measure using a Brookfield RVT viscometer. At 30°C the viscosity was 81,000 cps (averaged over three determinations) and at 40°C the viscosity was 94,333 cps (averaged over three determinations).

The composition can be applied using a long-throat actuator as described above (for spray application) or by cannula (for application to a specific area). A total of 4 spray shots is recommended. For application to a specific area by cannula rather than as a spray, the
35 preferred actuator is a stainless-steel cannula of about 73 mm in length, for example, the 215 stainless-steel cannula commercially available from Valois Pharmaceuticals, Inc.

The foregoing has outlined rather broadly the more pertinent and important features of the present invention. While it is apparent that the invention disclosed herein is well calculated to fulfill the objects stated above, it will be appreciated that numerous modifications and embodiments may be devised by those skilled in the art. Therefore, it is intended that the appended claims cover all such modifications.

5

10

15

20

25

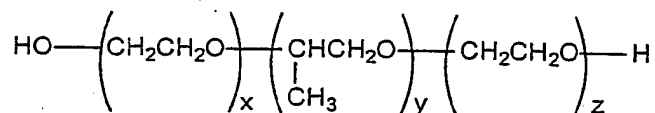
30

35

THE CLAIMS

What is claimed is:

1. A composition comprising a mucoadhesive, a local anesthetic or a pharmaceutically-acceptable salt thereof, and an opioid or a pharmaceutically-acceptable salt thereof.
2. The composition of claim 1, wherein an amount of the local anesthetic is within a range of from about 0.01 percent to about 0.5 percent of a total weight of the composition.
3. The composition of claim 1, wherein an amount of the opioid is within a range of from about 0.05 percent to about 1 percent of a total weight of the composition.
4. The composition of claim 1, wherein an amount of the mucoadhesive is within a range of from about 0.1 percent to about 40 percent of a total weight of the composition.
5. The composition of claim 1, wherein an amount of the mucoadhesive is within a range of from about 15 percent to about 25 percent of a total weight of the composition.
6. The composition of claim 1, wherein the mucoadhesive is a block copolymer of ethylene oxide and propylene oxide.
7. The composition of claim 1, wherein the mucoadhesive is a block copolymer of ethylene oxide and propylene oxide of a formula I:



I

wherein x is an integer having an average value ranging from about 2 to about 128; y is an integer having an average value ranging from about 14 to about 80; and z is an integer having an average value ranging from 2 to about 128.

8. The composition of claim 1, wherein the mucoadhesive is poloxamer 407.

9. The composition of claim 1, wherein the local anesthetic is selected from the group consisting of lidocaine, tetracaine, bupivacaine, prilocaine, mepivacaine, procaine, chlorprocaine, ropivacaine, dibucaine, etidocaine, benzocaine, a pharmaceutically-acceptable salt thereof, and a mixture thereof.

10. The composition of claim 1, wherein the local anesthetic is lidocaine or a pharmaceutically-acceptable salt thereof.

11. The composition of claim 1, wherein the opioid is morphine or loperamide or a pharmaceutically-acceptable salt thereof.

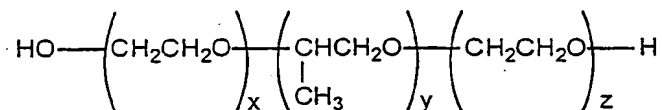
12. The composition of claim 1, wherein the opioid is morphine or a pharmaceutically-acceptable salt thereof.

13. A container adapted for topical application containing a composition comprising a mucoadhesive, a local anesthetic or a pharmaceutically-acceptable salt thereof, and an opioid or a pharmaceutically-acceptable salt thereof.

14. The container of claim 13, packaged in association with instructions, the instructions comprising: topically applying the composition onto a mucous membrane of a subject.

15. The container of claim 13, wherein the mucoadhesive is a block copolymer of ethylene oxide and propylene oxide.

16. The container of claim 13, wherein the mucoadhesive is a block copolymer of ethylene oxide and propylene oxide of a formula I:



I

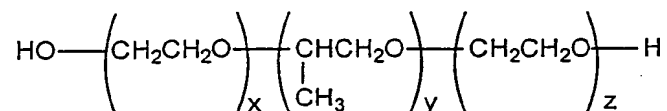
wherein x is an integer having an average value ranging from about 2 to about 128; y is an integer having an average value ranging from about 14 to about 80; and z is an integer having an average value ranging from 2 to about 128.

17. The container of claim 13, wherein the mucoadhesive is poloxamer 407.
18. The container of claim 13, wherein the local anesthetic is selected from the group consisting of lidocaine, tetracaine, bupivacaine, prilocaine, mepivacaine, procaine, chloroprocaine, ropivacaine, dibucaine, etidocaine, benzocaine, a pharmaceutically-acceptable salt thereof, and a mixture thereof.
19. The container of claim 13, wherein the local anesthetic is lidocaine or a pharmaceutically-acceptable salt thereof.
20. The container of claim 13, wherein the opioid is morphine or loperamide or a pharmaceutically-acceptable salt thereof.
21. The container of claim 13, wherein the opioid is morphine or a pharmaceutically-acceptable salt thereof.
22. A method of inducing local anesthesia in a subject comprising topically applying a composition comprising a mucoadhesive, a local anesthetic or a pharmaceutically-acceptable salt thereof, and an opioid or a pharmaceutically-acceptable salt thereof to a subject.
23. The method of claim 22, wherein the composition is applied to the buccal mucous membrane.
24. The method of claim 22, wherein an amount of the local anesthetic is within a range of from about 0.01 percent to about 0.5 percent of a total weight of the composition.
25. The method of claim 22, wherein an amount of the opioid is within a range of from about 0.05 percent to about 1 percent of a total weight of the composition.
26. The method of claim 22, wherein an amount of the mucoadhesive is within a range of from about 0.1 percent to about 40 percent of a total weight of the composition.

27. The method of claim 22, wherein an amount of the mucoadhesive is within a range of from about 15 percent to about 25 percent of a total weight of the composition.

28. The method of claim 22, wherein the mucoadhesive is a block copolymer of ethylene oxide and propylene oxide.

29. The method of claim 22, wherein the mucoadhesive is a block copolymer of ethylene oxide and propylene oxide of a formula I:



I

wherein x is an integer having an average value ranging from about 2 to about 128; y is an integer having an average value ranging from about 14 to about 80; and z is an integer having an average value ranging from 2 to about 128.

30. The method of claim 22, wherein the mucoadhesive is poloxamer 407.

31. The method of claim 22, wherein the local anesthetic is selected from the group consisting of lidocaine, tetracaine, bupivacaine, prilocaine, mepivacaine, procaine, chlorprocaine, ropivacaine, dibucaine, etidocaine, benzocaine, a pharmaceutically-acceptable salt thereof, and a mixture thereof.

32. The method of claim 22, wherein the local anesthetic is lidocaine or a pharmaceutically-acceptable salt thereof.

33. The method of claim 22, wherein the opioid is morphine or loperamide or a pharmaceutically-acceptable salt thereof.

34. The method of claim 22, wherein the opioid is morphine or a pharmaceutically-acceptable salt thereof.

THIS PAGE BLANK (USPTO)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
3 January 2002 (03.01.2002)

PCT

(10) International Publication Number
WO 02/000195 A3

(15) International Patent Classification⁷: **A61K 9/12, 9/00**

(21) International Application Number: **PCT/US01/20322**

(22) International Filing Date: **26 June 2001 (26.06.2001)**

(25) Filing Language: **English**

(26) Publication Language: **English**

(30) Priority Data:
60/222,164 26 June 2000 (26.06.2000) US

(71) Applicant: **EPICEPT CORPORATION [US/US]; 270
Sylvan Avenue, Englewood Cliffs, NJ 07632 (US).**

(72) Inventors: **WILLIAMS, Robert, O.; 4514 Rapid Springs
Cove, Austin, TX 78746 (US). ZHANG, Feng; 4559 Aven-
ue A #204, Austin, TX 78751 (US). KOLENG, John, J.;
3002 Boxdale Drive, Austin, TX 78757 (US). PASTER-
NAK, Gavril, W.; Apartment 21M, 500 East 83rd Street,
New York, NY 10028 (US). KOLESNIKOV, Yuri, A.; 4
Esmond Place, Tenafly, NJ 07670 (US).**

(74) Agents: **ABRAMS, Samuel, B. et al.; Pennie & Edmonds
LLP, 1155 Avenue of the Americas, New York, NY 10036
(US).**

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

- *with international search report*
- *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

(88) Date of publication of the international search report:
15 August 2002

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: **METHODS AND COMPOSITIONS FOR TREATING PAIN OF THE MUCOUS MEMBRANE**

(57) Abstract: Compositions useful for long-lasting pain relief from mucosal damage, such as mucosal inflammation, abrasions, ulcerations, lesions, trauma and incisions, without significant systemic absorption. The compositions of the invention are particularly suitable for application to the mucous membrane of the nasal cavity and bucal cavity. To relieve pain, the compositions or the invention are topically applied directly to the affected area.

WO 02/000195 A3

INTERNATIONAL SEARCH REPORT

International Application No.

/US 01/20322

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K9/12 A61K9/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 578 315 A (CHIEN YIE W ET AL) 26 November 1996 (1996-11-26) column 5, line 66 -column 6, line 41; claims 1,2; example 1	1,2,4,5, 9,10
Y	US 5 112 620 A (REPKA MICHAEL A ET AL) 12 May 1992 (1992-05-12) column 1, line 31-56 column 4, line 31-64; claims 1-4	1,2,4,5, 9,10
Y	US 5 948 389 A (STEIN CHRISTOPH) 7 September 1999 (1999-09-07) column 3, line 25-37 column 7, line 29-33; claims 1-6	1,2,4,5, 9,10

☐ Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

& document member of the same patent family

Date of the actual completion of the international search

10 June 2002

Date of mailing of the international search report

18/06/2002

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Uh1, M

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US91/20322

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
US 5578315	A	26-11-1996	AU	1100295 A	19-06-1995
			EP	0731679 A1	18-09-1996
			JP	9506092 T	17-06-1997
			WO	9515137 A1	08-06-1995
<hr/>					
US 5112620	A	12-05-1992	US	5714165 A	03-02-1998
<hr/>					
US 5948389	A	07-09-1999	NONE		
<hr/>					

THIS PAGE BLANK (USPTO)